

Supplementary material for “Dynamical correlations in the escape strategy of Influenza A virus”

Lorenzo Taggi^{1,2}, Francesca Colaiori^{1,3}, Vittorio Loreto^{1,4} and Francesca Tria⁴

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¹Sapienza University of Rome, Physics Department, P.le A. Moro 5, 00185 Rome, Italy

² Max Planck Institute for Mathematics in the Sciences, Inselstr. 22, 04103 Leipzig, Germany

³ CNR-ISC, P.le A. Moro 5, 00185 Rome, Italy

⁴ ISI Foundation, Via Alassio 11/c, 10126, Torino, Italy

1 Properties of the Epistatic Immunity Set

1.1 Size

As discussed in the main text, in our model the immunity set $I_n(\vec{v})$ is defined as the number of strings that do not contain two adjacent mutations with respect to a given string \vec{v} (we consider “adjacent” also the first and the last bit of every string),

$$I_n(\vec{v}) = \{ \vec{z} \in H_n : z_i \neq v_i \Rightarrow z_{|i+1|_n} = v_{|i+1|_n} \ \forall i \}. \quad (1)$$

Since cross-immunity, as defined in (1), is only sensible to differences between strains, $I_n(\vec{v})$ is invariant under translation on the hypercube with periodic boundary conditions. In order to see this, we can define a sort of translational operator acting on the space of sequences,

$$\mathcal{X}_{\vec{c}}(\cdot) = \vec{c} \ \underline{\vee} \ \cdot, \quad (2)$$

where \vec{c} is a generic strain and “ $\underline{\vee}$ ” is the *XOR* operator. Both the EI-sets and the hamming distance are invariant to it:

$$\vec{v}_2 \in I_n(\vec{v}_1) \Leftrightarrow \mathcal{X}_{\vec{c}}(\vec{v}_2) \in I_n(\mathcal{X}_{\vec{c}}(\vec{v}_1)), \quad (3)$$

$$d(\vec{v}_1, \vec{v}_2) = d(\mathcal{X}_{\vec{c}}(\vec{v}_1), \mathcal{X}_{\vec{c}}(\vec{v}_2)) \ \forall \vec{c}. \quad (4)$$

Therefore $I_n(\vec{v}) = \mathcal{X}_{\vec{v}}(I_n(\vec{0}))$. Then, in order to characterize the static properties of $I_n(\vec{v})$, we can take the null vector $\vec{0}$ as generating strain for the immunity set without loss of generality. Let us now compute the cardinality of the immunity

set. In order to do this, we first compute the cardinality of the EI set “without boundary conditions” (EISNB), defined as:

$$I_n^{NB}(\vec{v}) = \{ \vec{z} \in H_n : z_i \neq v_i \Rightarrow z_{i+1} = v_{i+1} \quad \forall i \in 0, 1, \dots, n-1 \}, \quad (5)$$

and then we show that the cardinality of (1) is a linear combination of cardinalities of EISNB sets.

Lemma 1.1. Let us call $B(n)$ the cardinality of the EISNB. This number follows the recursive law,

$$B(n) = B(n-1) + B(n-2),$$

with initial conditions $B(0) = 1$ and $B(1) = 2$.

Proof.

- $I_1^{NB}(\vec{0}) = \{(0), (1)\} \Rightarrow B(1) = 2$.
- $I_2^{NB}(\vec{0}) = \{(0, 0), (1, 0), (0, 1)\} \Rightarrow B(2) = 3$.
- Let's consider the set $I_n^{NB}(\vec{0})$ for a generic dimension n . This set is equivalent to the union of the two disjoint sets C_n and D_n , which are respectively defined as the set of all strings belonging to $I_n^{NB}(\vec{0})$ with the first bit equal to 1 and as the set of all strings belonging to $I_n^{NB}(\vec{0})$ with the first bit equal to 0:

$$C_n = \{ \vec{v} \in H_n \text{ s.t. } \vec{v} = (1, 0, \vec{c}), \quad \vec{c} \in I_{n-2}(\vec{0}) \}, \quad (6)$$

$$D_n = \{ \vec{v} \in H_n \text{ s.t. } \vec{v} = (0, \vec{c}), \quad \vec{c} \in I_{n-1}(\vec{0}) \}. \quad (7)$$

In equation (6) we have considered that, by definition of EISNB, if the first bit is mutated, the second one cannot be mutated. It's easy to see that the cardinality of the first set is equal to $B(n-2)$ and that the cardinality of the second one is equal to $B(n-1)$. Being the two sets disjoint, $B(n) = B(n-1) + B(n-2)$.

□

Thus, the cardinality of the EISNB follows the well known Fibonacci rule. We will use this result to determine the cardinality of the Epistatic Immunity Set.

Lemma 1.2. Let us call $S(n)$ the cardinality of the Epistatic Immunity Set. This number follows the following recursive law,

$$S(n) = S(n-1) + S(n-2),$$

with initial conditions $S(2) = 3$ and $S(3) = 4$.

Proof. As for the previous lemma, the proof is by induction.

- $I_2(\vec{0}) = \{(0, 0), (1, 0), (0, 1)\} \Rightarrow S(2) = 3;$
- $I_3(\vec{0}) = \{(0, 0, 0), (1, 0, 0), (0, 1, 0), (0, 0, 1)\} \Rightarrow S(3) = 4;$
- We observe that the following relation between the EI set and the EISNB holds:

$$I_n(\vec{0}) = I_n^{NB}(\vec{0}) \setminus \{ \vec{z} \in I_n^{NB}(\vec{0}) : \vec{z} = (1, 0, \vec{c}, 0, 1), \vec{c} \in I_{n-4}^s(\vec{0}) \}. \quad (8)$$

Then,

$$S(n) = B(n) - B(n-4). \quad (9)$$

Applying Lemma 1.1 to equation (9) one gets:

$$B(n) - B(n-4) = B(n-1) + B(n-2) - B(n-5) - B(n-6). \quad (10)$$

Then, collecting the terms properly and using again equation (9), we finally find the desired relation:

$$S(n) = S(n-1) + S(n-2).$$

□

The sequence $S(n) = S(n-1) + S(n-2)$, under the initial condition specified by the previous lemma, is called *Lucas sequence*. As for the Fibonacci sequence, the fraction of two consecutive numbers of the Lucas sequence converges asymptotically to the value $\Phi = \frac{1+\sqrt{5}}{2}$, which is well known as the *Golden Ratio*. In particular it is easy to show that $S(n) = \Phi^n + (1-\Phi)^n \sim \Phi^n$.

1.2 Density

We define the *Epistatic density function* as the ratio between the number of strings, $L(n, i)$, contained in $I_n(\vec{0})$ and having hamming distance i from $\vec{0}$ and the number $V(n, i)$ of strings having hamming distance i from $\vec{0}$:

$$\rho_n(i) := \frac{L(n, i)}{V(n, i)}. \quad (11)$$

This function gives an idea of how the elements of the epistatic immunity set are distributed on the hypercube. It is easy to check that $L(n, i) = \binom{n-i+1}{i} - \binom{n-i-1}{i-2}$. The first term represents the number of strings not containing two adjacent ones; the second term represents the number of strings not containing

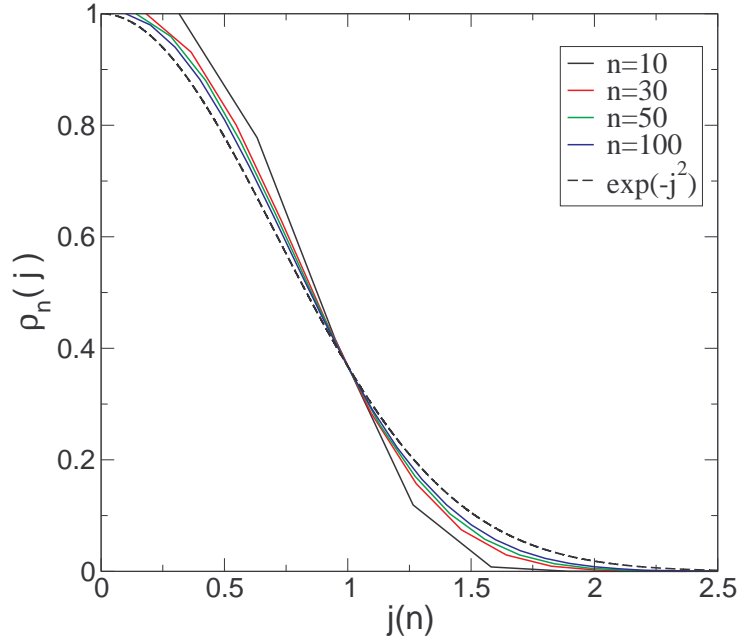


Figure 1: Epistatic density function computed numerically directly from definition (11) for $n = 10, 30, 50, 100$. The densities are plotted as function of $j(n) = i/\sqrt{n}$, where i is the length. As n increases, the epistatic density function converges to the well defined function $\rho_\infty(j) = \exp(-j^2)$.

any pairs of adjacent ones, but with the first and the last bit both equal to one. Thus the second term takes into account the effect of the periodic condition in definition (1). The denominator is simply $V(n, i) = \binom{n}{i}$. The density function (11), computed numerically, is represented for different values of n and plotted as function of i/\sqrt{n} in Fig. 1. We see that $\rho_n(i)$ can be approximated as

$$\rho_n(i) \simeq \exp\left(-\frac{i^2}{n}\right), \quad (12)$$

and, substituting $j = i/\sqrt{n}$, we get

$$\rho_n(j) \simeq \exp(-j^2). \quad (13)$$

Therefore, the epistatic immunity set covers an area of the hypercube whose size grows proportionally to \sqrt{n} . In this area, the density of strings satisfies equation (12). We now prove analytically validity of approximation (12) in the

range $i \leq \sqrt{n}$.

$$\begin{aligned}
\rho_n(i) &= \frac{(n-i)! \cdot (n-i+1)!}{n! \cdot (n-2i+1)!} \left[1 - \frac{i \cdot (i-1)}{(n-i+1) \cdot (n-i)} \right] \\
&= \frac{(n-i) \cdot (n-i-1) \dots (n-2i+2)}{n \cdot (n-1) \dots (n-i+2)} [1 + O(i/n)^2] \\
&= (1 - \frac{i}{n}) \cdot (1 - \frac{i}{n-1}) \dots (1 - \frac{i}{n-(i-2)}) \cdot (1 + O(i/n)^2) \\
&= (1 - i/n + O(i/n)^2)^{i-1} \cdot (1 + O(i/n)^2).
\end{aligned} \tag{14}$$

Using the expansion:

$$(1+x)^{i-1} = \sum_{l=0}^{i-1} \binom{i-1}{l} x^l, \tag{15}$$

one gets:

$$\begin{aligned}
&= \left[\sum_{l=0}^{i-1} \binom{i-1}{l} [O(i/n)^2 - i/n]^l \right] \cdot (1 + O(i/n)^2) \\
&= \left[\sum_{l=0}^{i-1} \binom{i-1}{l} [-(i/n)^l + O(i/n)^{l+1} + O(i/n)^{l+2} \dots O(i/n)^{2l}] \right] \cdot (1 + O(i/n)^2) \\
&= \{1 + [-\frac{i^2}{n} + O(\frac{i}{n})] + [\frac{i^4}{2!n^2} + O(\frac{i^3}{n^2})] + [-\frac{i^6}{3!n^3} + O(\frac{i^5}{n^3})] + \dots\} \cdot (1 + O(i/n)^2).
\end{aligned} \tag{16}$$

Then, substituting $j = i/\sqrt{n}$ and considering $j \leq 1$, we get equation (13):

$$\begin{aligned}
\rho_n(j) &= O(\frac{j}{\sqrt{n}}) + 1 - j^2 + \frac{j^4}{2!} - \frac{j^6}{3!} \dots \\
&= \exp(-j^2) + O(\frac{j}{\sqrt{n}}).
\end{aligned} \tag{17}$$

2 Numerical estimate of $m(n)$

In the main text we introduced the quantities $m(n)$ and $M(n)$ in order to investigate how the introduction of a correlated rule for cross-immunity shapes the EIS. $m(n)$ is defined as the minimum number of strings needed to cover with their immunity sets the whole sequences space; $M(n)$ is the maximum number of distinct strings that can be accommodated in the space of sequences still leaving some strings out of their EIS. Essentially, in the two cases the set of strings that realizes the minimum (maximum) will be such to minimize (maximize) the overlap among immunity sets. In the main text we have computed $M(n)$

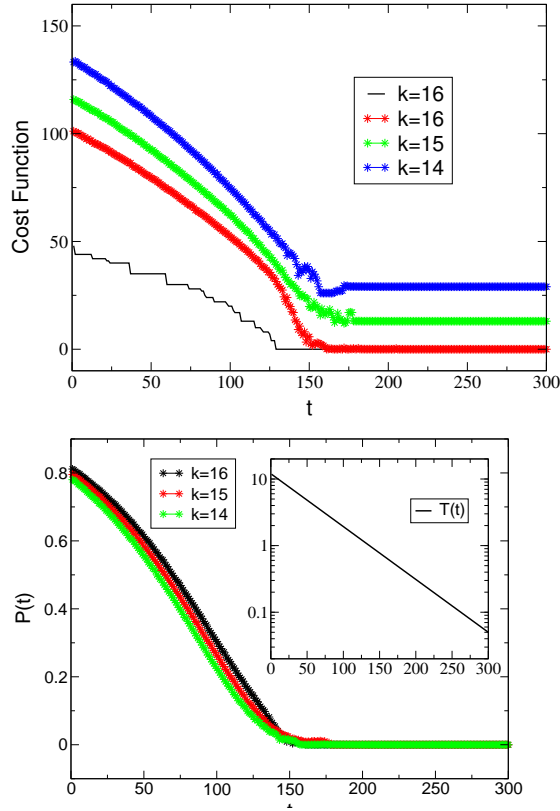


Figure 2: **Top.** Cost function averaged over several realizations for the same temperature $T(t)$ and for $k = 14, 15, 16$ and $n = 10$ (dots); minimum value of the cost function obtained until time t for $k = 16$ and $n = 10$ (continuous line). **Bottom.** The acceptance probability $P(t)$, which is equal to the fraction of solutions accepted at temperature $T(t)$. **Inset.** The thermal function adopted for these simulations, $T(t) = T_0 \cdot \alpha^t$, with $\alpha \simeq 0.982$ and $T_0 = 15$.

analytically and we have provided analytical and numerical estimates for $m(n)$. In order to compute the numerical estimate for $m(n)$ we adopted a Simulated Annealing approach [1].

We first notice that an exhaustive search of the solution would not be possible because the space of the infection sets is too big: for instance, the number of possible infection sets with cardinality 16 in a space of dimension 10 is $\binom{2^n}{k} = \binom{2^{10}}{16} \sim 10^{35}$. We instead proceeded as follows: we fix a value k for the number of elements of the infection set A and we search for a configuration which minimizes the cost function $E_{n,k}(A_k) = 2^n - |I_n(A_k)|$ (we denominate A_k any infection set with cardinality k). Of course, $E_{n,k}(A_k) \geq 0$ for all k : the smallest k for which we obtain $E_{n,k}(A_k) = 0$ for some set A_k is the numerical estimate for $m(n)$, $m_N(n)$, and the relative set is one of the possible A_{min} . For

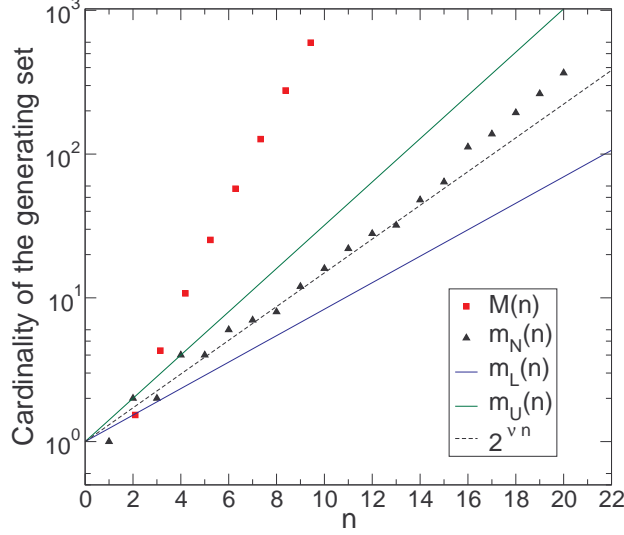


Figure 3: Numerical estimate of $m(n)$, $m_N(n)$, along with its lower and upper bound, and the value of $M(n)$ as a function of n . The dotted line represents the function $2^{\nu n}$, with $\nu = 0.399 \pm 0.002$, which has been used to fit the first 15 values of $m_N(n)$.

fixed values of n and k we start from a random choice of the infection set A_k and we modify a randomly selected bit of a randomly selected string in A_k . Then we compute the new cost function $E_{n,k}(A'_k)$ and

- if $E_{n,k}(A'_k) < E_{n,k}(A_k)$, then A_k is replaced by A'_k with probability 1;
- if $E_{n,k}(A'_k) \geq E_{n,k}(A_k)$, then A_k is replaced by A'_k with probability $P(\Delta E) = \exp(-\Delta E/T(t))$.

We iterate this procedure $R(t)$ times for every value of the temperature $T(t)$. Afterwards, temperature is updated with the rule $T(t+1) = \alpha \cdot T(t)$, where $0 < \alpha < 1$. The number of iterations performed for every temperature value, $R(t)$, is chosen to grow exponentially with t . In fact, recalling the analogy with Statistical Mechanics [1], lower is the temperature, larger is the time a body that can exchange heat with a thermal bath needs to reach the thermal equilibrium. In Fig. 2 (top) we report the behaviour of the cost function, averaged over all the iterations performed at the same temperature $T(t)$, as function of t . In Fig. 2 (bottom) we report the fraction of accepted solutions at time t as well as the function $T(t)$ considered. When the average cost function and the minimum cost function stop decreasing and remain constant, a local minimum is reached. The results obtained for the cardinality of the generating set are reported in Fig. 3 for values of n up to $n = 20$. We also report the upper and lower bounds for $m(n)$. Due to the high computational complexity of the problem

(the number of local minima of the cost function and the size of the solutions space both grow very fast with n and k), our numerical estimate of $m(n)$ tends to be rougher for higher values of n .

3 Cluster structure of the EIS

In the main text we have studied the cluster structure of the EIS. Let us first recall that the immunity set, $I_n(\vec{v})$, of a single string \vec{v} is a connected set. Without loss of generality we consider $\vec{v} = \vec{0}$ since the $I_n(\vec{v})$ is invariant under translation on the hypercube with periodic boundary conditions, through the translation operator (2). We can think $I_n(\vec{0})$ as the union of the disjoint sets, $I_n(\vec{0}) = \cup_{i=0}^n N_i$, with

$$N_i \equiv \{ z \in I_n(\vec{0}) : d_h(\vec{0}, \vec{z}) = i \}. \quad (18)$$

For each $\vec{z}_i \in N_i$ there is always a nearest neighbor contained in N_{i-1} such that $d_h(\vec{z}_i, \vec{z}_{i-1}) = 1$. This implies that, for each string in $I_n(\vec{0})$, it always exists a sequence of nearest neighbors to connect that string to $\vec{0}$, i.e. $I_n(\vec{v})$ is a connected set.

Starting from this result, in the main text we have shown that the EIS is always connected, though not simply connected. In fact, when k strings are drawn at random, there exists a threshold for $k = \lceil n/2 \rceil$ above which the complementary EIS (CEIS) can be broken down in clusters. This is due to the fact that we need to choose at least $\lceil n/2 \rceil$ strings in order to generate an EIS that contains “holes”, as it is shown in the sketch in Figure 4 (bottom). An example is given by the following infection set:

$$\begin{aligned} & (1, 1, 0, 0, 0, 0) \\ & (0, 0, 1, 1, 0, 0) \\ & (0, 0, 0, 0, 1, 1) \end{aligned}$$

The string $(0, 0, 0, 0, 0, 0)$ is not contained into the EIS generated by this set, on the contrary of all its neighbours. Therefore, the string alone constitute a cluster of the CEIS. However, other infection sets can generate CEIS featuring a much more complex cluster structure.

Figure 4 (top) shows the average number of connected clusters in the CEIS (divided by the maximum value for each n) as a function of the rescaled variable:

$$k'(n) = \frac{k}{2^{\eta n}} \cdot \frac{1}{1 - 2^{-\gamma \cdot n}}, \quad (19)$$

where the exponent $\gamma \simeq 0.12$ estimates the finite size scale effects and $2^{-\eta n}$ is the fraction of strings contained into the immunity set of a single strain with $\eta = 1 - \ln_2 \phi \sim 0.306$. Therefore the normalized number of connected clusters in the CEIS can be rescaled on a single master curve as n increases, thanks to a suitable rescaling of k .

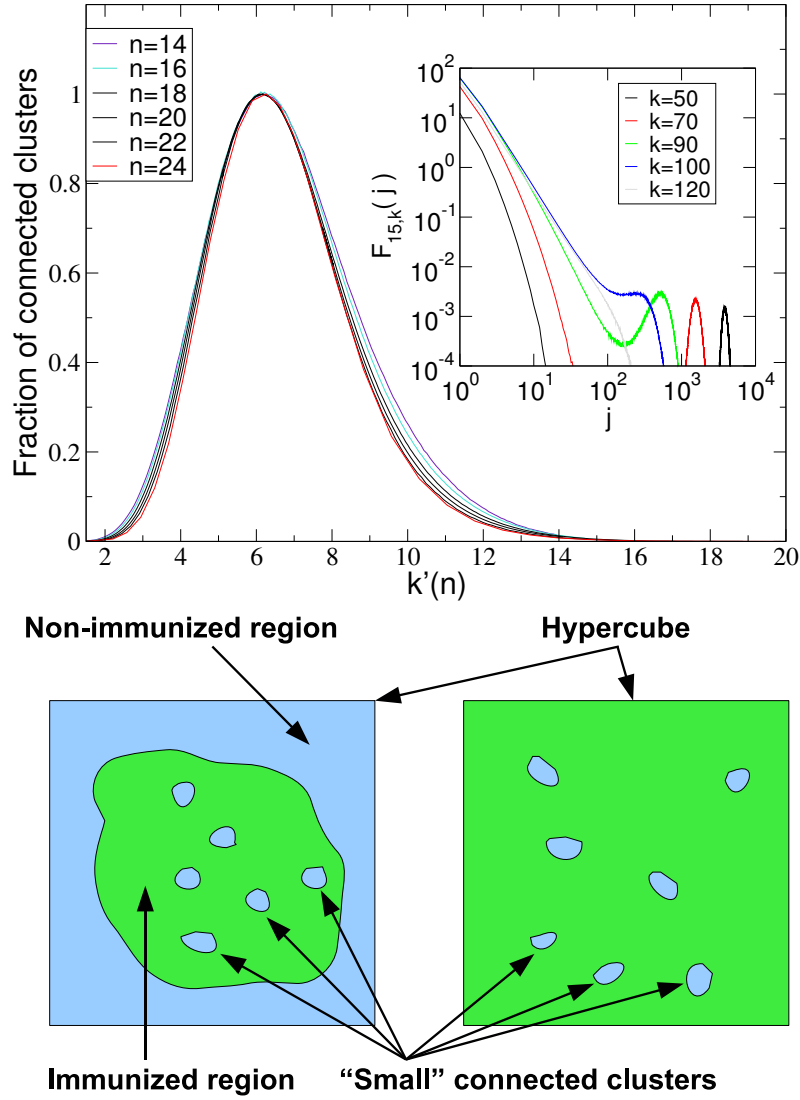


Figure 4: **Top** Average number of connected clusters, $F_{15,k}(j)$, composing the CEIS as a function of $k'(n)$ as defined in the text. For each value of n the functions plotted have been divided by their maximum value. The functions collapse into a well defined function, independent of n , as n increases. **Inset.** Distributions $F_{15,k}(j)$ for several values of k . For $k < 90$ the functions feature two disjoint peaks with the rightmost peak, whose area is equal to 1, moves to the left as k increases. For $k > 90$ the two peaks merge. **Bottom** Sketch of the topology of the immunized (green) and non-immunized (blue) region of the sequence space. *Left*: the set CEIS is composed by one *big* connected cluster, corresponding to a non-immunized region of the hypercube, and many *small* connected clusters, corresponding to “holes” contained into the EIS. *Right*: the whole hypercube is immunized apart from a few non-immunized clusters.

A more detailed description of the cluster structure of the CEIS can be obtained by investigating the dependence on n and k of the average size of the connected components composing it. To this end we define the distribution functions $F_{n,k}(j)$ as follows. $F_{n,k}(j)$ are defined as the average number of connected clusters, with cardinality j , generated by an infection set with k randomly drawn strains. In Fig 4 (inset of the top panel) we report the distributions for $n = 15$ and several values of k . It turns out that, for values of k not too large, the complementary set is composed by one big connected cluster and many small connected clusters. In fact the distributions exhibit two disjoint peaks: one centered on a large value of j , due to the contribution of the *big* cluster, and one centered on small values of j , given by the contribution of the *small* clusters. Further analysis reveals that the area of the former peak is always equal to 1 and that for every choice of the infection set there is always only one big cluster. On the other hand, the number of the small clusters is not fixed and depends on the infection set. On the contrary, for larger values of k , only the small connected clusters remain: increasing k the rightmost peak disappears, moving on the left and merging with the leftmost peak. As sketched in Fig. 4 (bottom), it is reasonable to interpret the big cluster as a region of the hypercube which has not been immunized yet and the small connected clusters of the CEIS as *holes* contained into the immunized region of the hypercube. This cluster structure of the CEIS could have a strong impact on the underlying virus-host interaction, which could be investigated through a more realistic simulation of the virus-host dynamics.

References

- [1] S. Kirkpatrick, C. D. Gelatt and M. P. Vecchi, Science, **220**, 671-680, (1983).